REMARKS

After amendment herein, claims 1-8, 13-21, 23, 25-29, 31 and 32 are pending. Claims 1, 8, 13, 25, 26, 29, 31 and 32 have been amended. Support for these amendments can be found at least at page 28 (pharmaceutically acceptable salt), page 30, lines 6 to 12 (solvates), pages 12 to 22 of the specification (list of substituents), page 9 (definition of C_{3-20} heterocyclyl), page 10-11 (definition of C_{5-20} aryl), original claims 11 and 12 ("where –X'-R"-X- is –O-$(CH_2)_n$-O-, where n is 8 to 12), and pages 96-100 (Example 27) (list of proliferative diseases). Claims 9-12 and 30 have been canceled herein. No new matter has been added by these amendments.

Rejections Under Section 112, Second Paragraph

Claims 1-21, 23 and 25-32 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for varying reasons. The phrase "and salts, solvates, chemically protected forms" was found to be indefinite because it was not in proper Markush form. Applicants have amended the claims 1 and 8 to correct this error and request that this rejection be withdrawn.

In addition, the terms "chemically protected forms," "optionally substituted," "C_{3-20} heterocyclyl," "C_{5-20} aryl," "X," and "e.g" were found to be unclear and/or indefinite. Applicants have amended claims 1, 8, 26 and 29, as needed, to address the rejections. "Chemically protected forms" and "e.g." were deleted; the substituents were delineated in the claims; the definitions of C_{3-20} heterocyclyl and C_{5-20} aryl from the specification were added to the claims; and "X" is now limited to oxygen. Applicants request that the rejections be withdrawn.

Claims 26 and 29 were rejected as being incomplete for omitting essential steps. Applicants have amended the claims to incorporate the steps necessary to complete the reactions and request that the rejection be withdrawn.

Claims 9-12 and 30 have been canceled so the rejection of those claims is moot. The remaining claims are dependent and therefore are allowable for at least the reasons discussed above. Applicants respectfully request that the rejections of these claims be withdrawn.

Rejections Under Section 112, First Paragraph

Claims 1-21, 23 and 25-32 were rejected under 35 U.S.C. § 112, first paragraph, as not enabled for solvates. The examiner asserts that applicants have not shown how one skilled in the art can arrive at a given solvate. In addition, the examiner asserts that arriving at a given solvate is

not routine experimentation because it is unpredictable and one cannot make any solvate of a given compound. For the reasons stated below, Applicants respectfully disagree with this conclusion and instead assert that the claims in their current form are fully enabled commensurate with their scope.

The test for enablement is whether the disclosure, when filed, contained sufficient information to enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. MPEP 2164.01.

> The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

MPEP 2164.08 (emphasis added).

"In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure)." MPEP 2164.04. "[I]t is incumbent upon the Patent Office, whenever a rejection [for lack of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

In this case, the examiner has not met the initial burden of establishing a reasonable basis for doubting the enablement of the claimed invention. The examiner has not provided any evidence that one of ordinary skill in the art would not be able to form the claimed solvates without undue experimentation. The mere failure to include working examples that describe formation of solvates of the claimed compound does not, as the examiner purports, mean that these forms of the compound do not exist.

In general, the disclosure of the novel compound of the claimed invention is more than sufficient to enable those having ordinary skill in the art to make and use the compound as well as any solvates thereof. Applicants respectfully submit that one of ordinary skill in the art would be capable of making a solvate of the claimed compound without undue experimentation, especially given the level of ordinary skill in the art. Thus, it is applicants' position that the scope of enablement provided in the specification bears a more than "reasonable correlation" to the scope of the pending claims.

Moreover, contrary to the examiner's position, the specification specifically teaches solvates of the claimed compound where the solvent adds across the imine bond of the pyrrolobenzodiazepine moiety. If the solvent is water or an alcohol, these solvates can be called the carbinolamine and carbinolamine ether forms of the pyrrolobenzodiazepine. (Specification at page 30, line 6 to page 31, line 3). Moreover, one of ordinary skill in the art would have known that any nucleophilic solvent, such as thiols and amines, is capable of forming such a solvate. (Specification at page 31, lines 4-9).

Thus, applicants respectfully submit that the claims are fully enabled by the specification and request that the rejection be withdrawn.

Claim 25 is also rejected as not enabled for the treatment of a proliferative disease generally. Without acquiescing to the propriety of the rejection, applicants have amended claim 25 to indicate that the proliferative disease is selected from leukemia, melanoma, lung cancer, renal cancer, colon cancer, CNS cancer, and ovarian cancer. The specification provides enablement for treating a proliferative disease selected from the above list in Example 27 of the specification where compounds of the present invention were tested in an *in vitro* cytotoxicity assay using leukemia cells. In addition, the compounds of the present invention were tested in a National Cancer Institute *in vitro* cytoxicity screen consisting of approximately 60 human tumor cell lines, including lung cancer, renal cancer, colon cancer, melanoma, CNS caner, ovarian cancer and leukemia. The compounds of the present invention were shown to be effective against these types of cancer as shown by the data at pages 99-100 of the specification. Thus, applicants respectfully request withdrawal of the rejection of claim 25.

Rejections Under Section 102

Claims 8, 10 and 18-21 were rejected under § 102(b) as anticipated by Farmer et al. (Tetrahedron Letters (1988), 29(40), 5105-8). Applicants have amended claim 8 to indicate that

with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). Thus, it is not sufficient to state that a structural relationship where the length of a linking carbon chin is *per se* obvious. *Takeda*, 492 F.3d 1350.

Moreover, it is unpredictable and unobvious whether or not such changes in a pyrrolobenzodiazepine dimer would affect the ability of the compound to bind to DNA. The chance of chemical and structural differences causing decreased or eliminated ability to bind to DNA relative to those compounds disclosed by Smellie et al. is just as great as the chances of them causing enhanced or equal ability to bind to DNA. As discussed in Smellie et al., the length of the linker affects the ability of the compounds to cross-link DNA. (Smellie et al. at 8233.) "The results confirm that the *n* = 3 and 5 (i.e. odd *n*) homologues are the most efficient cross-linking agents, and show that **2a** prefers a 5'-**G**ATC sequence but cannot tolderate an additional base pair between the two separated guanines on adjacent strands. However, the more extended PBD dimer **2c** (*n* =5) favors a longer 5'=**G**AATC (≡ 5'-**G**ATTC) sequence but can also covalently cross-link the short 5'-**G**ATC site, albeit less efficiently, presumably through a folded-linker conformation adopted by the bound ligand." (Id.) Therefore, one of ordinary skill in the art would not have had a reasonable expectation of success that the elongate C8-linked dimers (having n = 8 to 12) would cross-link DNA.

In addition, the present application contains biological data for C8-linked dimers: 16a-16j (n=3 to 12). (Specification at pages 99-10.) From this data, it is clear that elongate C8-linked dimmers, where n is 8 to 12, are effective as anti-tumor agents. Compounds 16f (n=8) and 16g (n=9) have the lowest IC_{50} values. This could not have been predicted from the prior art which taught that compounds where n=3 and n=5 are good anti-tumor agents, but compounds where n=4 and n=6 are not. One of ordinary skill in the art would not have been motivated to modify the compounds of Smellie et al. to have linkers where n is 8 to 12 based on the teachings of the prior art. Further, it is especially surprising that a compound where n=8 is more effective than one where n=7, as shown in the data at pages 99-100. The prior art teaches away from such a finding. Smellie et al. and Bose et al. both suggest that compounds with n equal to an odd number are more effective than compounds where n is an even number. (Smellie et al. at 8233 and Bose et al. at 1520.) This is contrary to the data shown in the specification where the compound where n=8 is more effective that one where n=7. Again, one of ordinary skill in the art would not have been lead to the claimed compounds where n is 8 to 12 based on these teachings.

the dimer is linked by a $-O-(CH_2)_n-O-$ group, wherein n is 8 to 12. Farmer et al. discloses compounds with a sulfur-containing group or an amino-containing group linking the dimer. Applicants respectfully submit that Farmer et al. does not teach the claimed compounds and request that the rejection be withdrawn.

Claim 10 was canceled and claims 18-21 are dependent on claim 8 and patentable for at least the above reasons. Applicants therefore request that the rejection be withdrawn.

Claims 8-11 and 18-21 were rejected under § 102(b) as anticipated by Bose et al. (Journal of the Chemical Society, Chemical Communications (1992), (20), 1518-20). Applicants have amended claim 8 to indicate that the dimer is linked by a $-O-(CH_2)_n-O-$ group, wherein n is 8 to 12. Bose et al. teach compounds with a linker having 3 to 6 carbon atoms, not compounds with a linker having 8 to 12 carbon atoms. Applicants respectfully submit that Bose et al. does not teach the claimed compounds and request that the rejection be withdrawn.

Claims 9-11 were canceled and claims 18-21 are dependent on claim 8 and patentable for at least the above reasons. Applicants therefore request that the rejection be withdrawn.

Rejections Under Section 103

Claims 8, 9, 11-16 and 18-21 were rejected under § 103(a) as unpatentable over Smellie et al. (Biochemistry (2003), 42(27), 8232-39). The examiner admits that Smellie et al. teach compounds that differ from the claimed compounds in the length of the linker between the PBD moieties. Smellie et al. teach a linker with no more than 6 carbons and the claimed compounds have longer linkers. The examiner asserts that it has long been established that a structural relationship that varies the size of a linking carbon chain is *per se* obvious.

Applicants respectfully submit that the claims as amended are not obvious over Smellie et al. Post-KSR, the Federal Circuit stated that: "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007). The Examiner has not provided any rationale why one of ordinary skill in the art would have modified the compounds of Smellie et al. to arrive at the claimed invention.

As pointed out by the Supreme Court recently, "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning

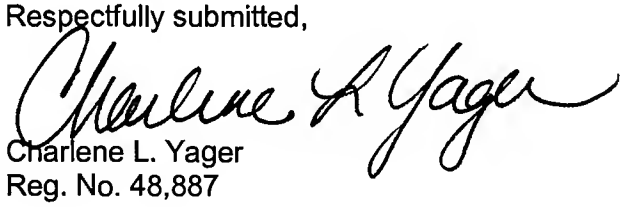
The Applicants respectfully submit that the examiner has not established either a motivation to modify the compounds of Smellie et al. to arrive at the claimed compound or a reasonable expectation of success that the claimed compound would have the same function as the compounds of Smellie et al. Thus, Applicants respectfully request withdrawal of the rejection over Smellie et al.

Claims 9, 11 and 12 were canceled herein. Claims 13-16 and 18-21 are dependent on claim 8 and patentable for at least the reasons discussed above. Applicants therefore request that that the rejection over Smellie et al. be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance. Should the examiner feel that any issues remain or wish to discuss anything further, the examiner is invited to contact the undersigned at the number below. No other fees are believed due in connection with the above response. Should any fee, in fact, be due, please charge Deposit Account No. 50-0842.

Respectfully submitted,



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